

PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 04 January 2001 (04.01.01)	
International application No.: PCT/GB00/02485	Applicant's or agent's file reference: HMJ03219WO
International filing date: 26 June 2000 (26.06.00)	Priority date: 24 June 1999 (24.06.99)
Applicant: STRATFORD, Peter, William et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International preliminary Examining Authority on:

13 November 2000 (13.11.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

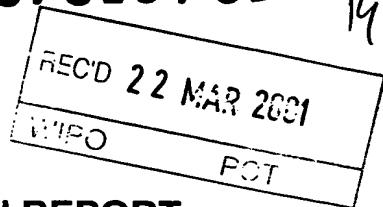
was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38
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10/018783

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference HMJ03219WO	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB00/02485	International filing date (day/month/year) 26/06/2000	Priority date (day/month/year) 24/06/1999	
International Patent Classification (IPC) or national classification and IPC A61F2/06			
Applicant BIOCOMPATIBLES LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 13/11/2000	Date of completion of this report 20.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bichlmayer, K-P Telephone No. +49 89 2399 2977



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02485

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*):

Description, pages:

1-23 as originally filed

Claims, No.:

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02485

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-22
 No: Claims

Inventive step (IS) Yes: Claims 1-22
 No: Claims

Industrial applicability (IA) Yes: Claims 1-22
 No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02485

Ad section V:

Reference is made to the following documents:

- D1: EP,A,0 920 843 (cited in the application)
- D2: US,A,5 344 426
- D3: WO,A,9 301 221
- D4: WO,A,9 830 615 (cited in the application)

1) Independent claim 1

D1 and D2 are considered as the most pertinent prior art documents disclosing a balloon catheter having a stent mounted thereon. According to D1, the stent is coated with a hydrogel polymer coating which serves a drug reservoir. The stent/balloon catheter combination of D2 is additionally provided with a separate protective sheath retaining the stent on the balloon surface thus avoid slipping off the stent before its correct placement in the blood vessel.

The subject-matter of the independent claim 1 is distinguished from D1 and D2 in that the exterior surface of the balloon and the stent is provided with a coherent coating comprising a film-forming polymer. By this coating the stent is retained on the balloon during the insertion and placement at a vessel constriction. Furthermore, lubricity of the kit may be enhanced. Therefore, the problem to be solved by the subject-matter of claim 1 can be considered as providing an alternative retaining means.

None of the available prior art documents discloses or suggests the solution provided by claim 1. Although D3 (and partly D4) describes film-forming polymer coatings, they concern coatings for prostheses, heart valves, catheters or artificial kidney membranes and are used to render the corresponding surfaces biocompatible. Therefore, D3 and D4 would not be considered by a skilled person when looking for means connecting a stent with a balloon catheter in the sense of retaining means.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02485

Therefore, the independent claim 1 meets the requirements of Art. 33(2) to (4) PCT.

2) Independent claim 15

The method claimed in independent claim 15 is distinguished from the closest prior art according to D1 (cf. on col. 11, lines 1 to 10) in that the balloon catheter and the stent mounted thereon is coated with a film-forming polymer and then is cured to leave a coherent film on the exterior surface of the stent and the balloon. Although D1 discloses that a stent placed over the balloon catheter is coated with noncomplexed hydrogel coating, it is important to note that only the stent becomes coated and therefore, the skilled person would no suggested by D1 to provide for means for retaining the stent on the balloon catheter by the features distinguishing claim 15 from D1. Since none of the remaining prior art documents relates to coating methods for a stent and a balloon acting as retaining means, claim 15 also meets the requirements of Art. 33(2) to (4) PCT.

3) Dependent claims 2 to 14 and 16 to 22

The dependent claims identified above concern specific embodiments of the inventive concept of the independent claims to which these claims are related and meet as such also the requirements of Art. 33(2) to (4) PCT.

Ad section VIII:

- 1) Dependent claim 9 lacks clarity within the meaning of Art. 6 PCT as it is related to claim 9 rather to one of the foregoing claims.
- 2) The guidewire lumen mentioned in dependent claim 13 has no antecedent in one of the foregoing claims such that claim 13 lacks clarity (Art. 6 PCT).

PENT COOPERATION TREATY

PCT

10/018783

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference HMJ03219W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/02485	International filing date (day/month/year) 26/06/2000	(Earliest) Priority Date (day/month/year) 24/06/1999
Applicant BIOCOMPATIBLES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of Invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/02485

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 920 843 A (BOSTON SCIENT CORP) 9 June 1999 (1999-06-09) cited in the application column 2, line 30 - line 44 column 11, line 27 - line 41 claims; figures ---	1-22
Y	WO 93 01221 A (BIOCOMPATIBLES LTD) 21 January 1993 (1993-01-21) cited in the application page 65, line 23 - line 27 claims; examples ---	1-22
X	WO 98 30615 A (BIOCOMPATIBLES LTD) 16 July 1998 (1998-07-16) cited in the application page 14, line 35 -page 15, line 8 claims; examples ---	1-22
-/-		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 September 2000

Date of mailing of the international search report

18/09/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kuehne, H-C

INTERNATIONAL SEARCH REPORTInternational Application No
P B 00/02485**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 344 426 A (LAU LILIP ET AL) 6 September 1994 (1994-09-06) claims; figures -----	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02485

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0920843	A	09-06-1999	US 5304121 A		19-04-1994
			CA 2098984 A		29-06-1992
			DE 69131486 D		02-09-1999
			DE 69131486 T		17-02-2000
			EP 0565604 A		20-10-1993
			ES 2137179 T		16-12-1999
			JP 6503984 T		12-05-1994
			WO 9211895 A		23-07-1992
			WO 9211896 A		23-07-1992
			US 5674192 A		07-10-1997
			US 5954706 A		21-09-1999
			US 5843089 A		01-12-1998

WO 9301221	A	21-01-1993	AT 190988 T		15-04-2000
			AU 666485 B		15-02-1996
			AU 2231092 A		11-02-1993
			AU 697066 B		24-09-1998
			AU 4030995 A		22-02-1996
			AU 7993198 A		08-10-1998
			AU 7993298 A		08-10-1998
			CA 2112411 A		21-01-1993
			DE 69230823 D		27-04-2000
			DE 69230823 T		27-07-2000
			EP 0593561 A		27-04-1994
			EP 0810239 A		03-12-1997
			ES 2144419 T		16-06-2000
			JP 11166015 A		22-06-1999
			JP 11166018 A		22-06-1999
			JP 11166150 A		22-06-1999
			JP 3030086 B		10-04-2000
			JP 7502053 T		02-03-1995
			US 6090901 A		18-07-2000
			US 5648442 A		15-07-1997
			US 5739236 A		14-04-1998
			US 5705583 A		06-01-1998
			US 5783650 A		21-07-1998
			EP 0818479 A		14-01-1998
			EP 0861858 A		02-09-1998

WO 9830615	A	16-07-1998	AU 5566698 A		03-08-1998
			AU 5567698 A		03-08-1998
			EP 0953001 A		03-11-1999
			EP 0977531 A		09-02-2000
			WO 9830181 A		16-07-1998
			ZA 9800174 A		11-01-1999

US 5344426	A	06-09-1994	US 5158548 A		27-10-1992
			US 5242399 A		07-09-1993

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00109 A1

(51) International Patent Classification⁷: A61F 2/06

(21) International Application Number: PCT/GB00/02485

(22) International Filing Date: 26 June 2000 (26.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99304975.8 24 June 1999 (24.06.1999) EP

(71) Applicant (for all designated States except US): BIO-COMPATIBLES LIMITED [GB/GB]; Chapman House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): STRATFORD, Peter, William [GB/GB]; Biocompatibles Limited, Frensham House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB). TAYLOR, Alistair, Stewart [GB/GB]; Biocompatibles Limited, Frensham House, Farnham Business Park, Weydon Lane, Farnham, Surrey GU9 8QL (GB). O'BYRNE, Vincent, James [IE/GB]; Biocompatibles Limited, Frensham House, Farnham Business Park, Weydon Lane, Farnham, Surrey

GU9 8QL (GB).

GU9 8QL (GB).

CLARKE, John, Tom [IE/IE]; Manulla, Castlebar, Co. Mayo (IE). HEALY, Denis, Dominic [IE/IE]; Biocompatibles CV Ireland Limited, Unit 13, Mervue Business Park, Galway (IE).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/00109 A1

(54) Title: BALLOON EXPANDABLE STENT

(57) Abstract: The present invention relates to a balloon expandable stent mounted on a balloon catheter, the entire assembly being overcoated with a coherent polymer coating, which is preferably substantially continuous over the circumference and, more preferably, axial length of the stent on the balloon. The polymer coating improves retention of the stent on the balloon during delivery and does not adversely effect the deployment characteristics, nor the balloon failure characteristics. The product is made by mounting the stent on the balloon and coating the assembly with a liquid coating composition containing a suitable polymer followed by curing of the coating. The polymer is biocompatible and preferably crosslinkable in the coating composition, and crosslinked in the final product. A suitable polymer is formed from monomers including a zwitterionic, preferably a phosphoryl choline, group, and monomers including a trialkoxysilyl group. Preferably the coated product is contacted with ethylene oxide to provide simultaneous sterilization and additional curing.

Balloon Expandable Stent

The present invention relates to balloon expandable stents for delivering into body lumens, in particular to stents formed from tubes, especially metal tubes. In particular this invention relates to means for retaining the stent on the balloon during storage and delivery of the stent through the body lumen prior to deployment, without adversely effecting the balloon strength or deployment of the stent.

Balloon expandable stent, either made from wires, or made from metal tubes which are cut or etched to form openings in the surface are crimped onto the balloon delivery device either as part of the manufacturing/assembly process, or immediately prior to use by a surgeon. Generally the stent is positioned over the balloon, sometimes on a sleeve which is positioned over the balloon, and is then crimped down onto the balloon. During the delivery procedure, when the delivery catheter carrying the stent is being maneuvered through body lumens, the stent is subjected to forces which may dislodge the stent from its desired position on the balloon.

Means have been described for retaining the stent in position on the balloon during delivery. For instance protrusions have been provided on the balloon, or the catheter near to the balloon, having shoulders above and/or below the stent location which bear against the stent when it is subjected to an axial force. Alternatively protrusions may be provided on the external surface of the balloon, or on a sleeve located between the stent and the balloon, which protrude into the holes through the wall of the stent. Again these protrusions have shoulders which may bear against the axially directed surfaces of those holes. However the procedures used to make such balloons tend to lead to weakening of the balloon wall and/or increase in the pressure required to inflate the balloon and/or require additional manufacturing steps and steps for careful positioning of the stent upon the balloon.

Other methods have involved the application of an adhesive layer between the stent and the balloon. However such layers may have an

adverse effect on balloon strength and/or inflation characteristics.

Furthermore it is difficult to ensure a good interfacial contact between the stent and the adhesive and/or adhesive and balloon. Such adhesives may also have an adverse effect on biocompatibility.

5 Other solutions to this problem have involved providing an external sheath surrounding the balloon when mounted on the catheter which must be retracted prior to deployment of the stent. This involves an extra step in the delivery process, increases the external diameter of the stent/delivery device combination and increases the likelihood of mechanical failure of the
10 delivery device.

15 The present invention seeks to solve the above problems. Some embodiments of the invention also improve the biocompatibility of the delivery device, and stent once delivered. Some embodiments of the invention may also provide improved lubricity of the delivery device during the stent delivery procedure.

In EP-A-0920843, a device is claimed which has a hydrogel coating on the external surface of an endoprosthesis for delivering a drug into the wall of a body lumen into which the prostheses is inserted. The prosthesis is for instance a stent. The stent may be coated when mounted on a balloon.
20 The sole example of hydrogel is a polyacrylic acid hydrogel, which appears to be crosslinked using a polyisocyanate crosslinker. It appears that the film is not continuous around the exterior surface of the balloon/stent combination.

25 According to the invention there is provided a new kit comprising a balloon catheter comprising a balloon at or near its distal end, and a stent mounted on the balloon, characterized in that in that the exterior surface of the balloon and stent are provided with a coherent coating comprising a film-forming polymer.

30 In the invention the coating is preferably continuous around the exterior surface of the balloon/stent, over at least a portion of the axial extent of that section. Preferably the coating is provided along the entire axial length of the stent, most preferably being continuous around the

circumference throughout the axial length. Preferably the coating extends beyond at least the distal stent end and preferably also the proximal stent end. It may extend along the exterior surface of the balloon catheter shaft proximal of the balloon.

5 The coating may comprise components other than the film forming polymer, for instance fillers, diluents, plasticisers, colouring agents, opacifying agents, pharmaceutically active agents, radioactive or other imaging agents etc. Often, however, the coating may consist essentially only of the film forming polymer.

10 The film forming polymer is preferably crosslinked to provide adequate coherent strength. Preferably the crosslinking of the polymer is achieved wholly or mainly after coating of the polymer on the surface which will be described in more detail in connection with the process below.

15 Preferably the polymer is biocompatible. Since the stent is primarily used in vascular lumens, the coating is preferably additionally hemo-compatible. The bio/hemo-compatibility should preferably persist during the delivery process and, preferably also, after the delivery process. Where the coating is biostable, that is not degraded after deployment of the device, the biocompatibility of the coating should persist throughout the 20 period during which the coating remains on the stent surface after deployment.

The biocompatibility is preferably achieved by the use of a polymer having pendent zwitterionic groups. Suitable groups X are for instance as defined below as groups of general formula III, V or VII.

25 Preferably a polymer having zwitterionic moieties is formed from radical polymerization of ethylenically unsaturated monomers including a zwitterionic monomer. Alternatively condensation polymers or preformed polymers derivatised by reaction with zwitterionic derivatising reagents may be used.

30 Preferably the zwitterionic monomer has the general formula I:

YBX

I

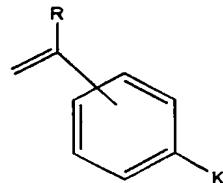
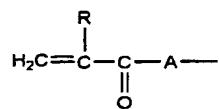
wherein

B is a straight or branched alkylene (alkanediyl), alkyleneoxaalkylene or alkylene oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X or Y contains a terminal carbon atom bonded to B, a valence bond;

5 X is a zwitterionic group; and

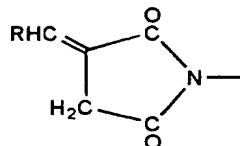
Y is an ethylenically unsaturated polymerisable group selected from

10

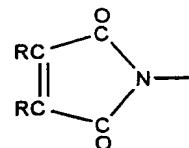


$\text{CH}_2=\text{C}(\text{R})-\text{CH}_2-\text{O}-$, $\text{CH}_2=\text{C}(\text{R})-\text{CH}_2\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R})\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R})-\text{O}-$,
 $\text{CH}_2=\text{C}(\text{R})\text{CH}_2\text{OC}(\text{O})\text{N}(\text{R}^1)-$, $\text{R}^2\text{OOC}-\text{CRC}(\text{O})-\text{O}-$, $\text{RCH}=\text{CHC}(\text{O})\text{O}-$,
 $\text{RCH}=\text{C}(\text{COOR}^2)\text{CH}_2-\text{C}(\text{O})-\text{O}-$,

15



and



wherein:

20 R is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group;

R^1 is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group or R^1 is $-\text{B}-\text{X}$ where B and X are as defined above; and

R^2 is hydrogen or a C_{1-4} alkyl group;

A is $-\text{O}-$ or $-\text{NR}^1-$;

25 K is a group $-(\text{CH}_2)_p\text{OC}(\text{O})-$, $-(\text{CH}_2)_p\text{C}(\text{O})\text{O}-$,

$-(\text{CH}_2)_p\text{OC}(\text{O})\text{O}-$, $-(\text{CH}_2)_p\text{NR}^3-$, $-(\text{CH}_2)_p\text{NR}^3\text{C}(\text{O})-$,

$-(\text{CH}_2)_p\text{C}(\text{O})\text{NR}^3-$, $-(\text{CH}_2)_p\text{NR}^3\text{C}(\text{O})\text{O}-$, $-(\text{CH}_2)_p\text{OC}(\text{O})\text{NR}^3-$,

$-(\text{CH}_2)_p\text{NR}^3\text{C}(\text{O})\text{NR}^3-$ (in which the groups R^3 are the same or different),

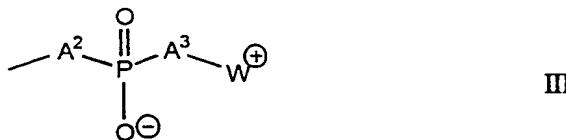
$-(\text{CH}_2)_p\text{O}-$, $-(\text{CH}_2)_p\text{SO}_3-$, or, optionally in combination with B, a valence bond

30 p is from 1 to 12; and

R^3 is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group.

In the zwitterionic monomer the general formula I, the zwitterionic group preferably has the general formula III

5



in which the moieties A^2 and A^3 , which are the same or different, are -
 O-, -S-, -NH- or a valence bond, preferably -O-, and W^+ is a group
 10 comprising an ammonium, phosphonium or sulphonium cationic group and a
 group linking the anionic and cationic moieties which is preferably a C_{1-12-}
 alkanediyl group,

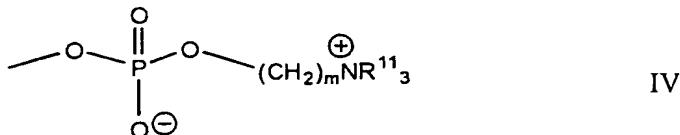
preferably in which W^+ is a group of formula
 $-W^1-N^+R^9_3$, $-W^1-P^+R^{10}_3$, $-W^1-S^+R^{10}_2$ or $-W^1-Het^+$ in which:
 15 W^1 is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally
 containing one or more ethylenically unsaturated double or triple bonds,
 disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene
 aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or
 20 alkylene cycloalkyl alkylene, which group W^1 optionally contains one or more
 fluorine substituents and/or one or more functional groups; and

either the groups R^9 are the same or different and each is hydrogen or
 alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or
 two of the groups R^9 together with the nitrogen atom to which they are
 attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or
 25 the three groups R^9 together with the nitrogen atom to which they are
 attached form a fused ring structure containing from 5 to 7 atoms in each
 ring, and optionally one or more of the groups R^9 is substituted by a
 hydrophilic functional group, and

the groups R^{10} are the same or different and each is R^9 or a group
 30 OR^9 , where R^9 is as defined above; or
 Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably
 nitrogen-, containing ring, for example pyridine.

Most preferably, the zwitterionic group of the formula III, has the general formula IV:

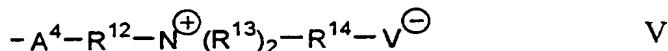
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where the groups R¹¹ are the same or different and each is hydrogen or C₁₋₄ alkyl, and m is from 1 to 4, in which preferably the groups R¹¹ are the same preferably methyl.

10 Alternatively, the zwitterionic group may be a betaine group (ie in which the cation is closer to the backbone), for instance a sulpho-, carboxy- or phospho-betaine. A betaine group should have no overall charge and is preferably therefore a carboxy- or sulpho-betaine. If it is a phosphobetaine the phosphate terminal group must be a diester, i.e., be esterified with an alcohol. Such groups may be represented by the general formula V

15



20 in which A⁴ is a valence bond, -O-, -S- or -NH-, preferably -O-; V is a carboxylate, sulphonate or phosphate diester(monovalently charged) anion;

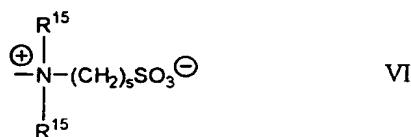
R¹² is a valence bond (together with A⁴) or alkanediyl, -C(O)alkylene- or -C(O)NHalkylene preferably alkanediyl, and preferably containing from 1 to 6 carbon atoms in the alkanediyl chain;

25 the groups R¹³ are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms or the groups R¹³ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 atoms; and

R¹⁴ is alkyanediyI of 1 to 20, preferably 1 to 10, more preferably 1 to 6 carbon atoms.

30

One preferred sulphobetaine monomer has the formula VI



5

where the groups R^{15} are the same or different and each is hydrogen or C_{1-4} alkyl and s is from 2 to 4.

Preferably the groups R^{15} are the same. It is also preferable that at least one of the groups R^{15} is methyl, and more preferable that the groups R^{15} are both methyl.

10

Preferably s is 2 or 3, more preferably 3.

Alternatively the zwitterionic group may be an amino acid moiety in which the alpha carbon atom (to which an amine group and the carboxylic acid group are attached) is joined through a linker group to the backbone of the biocompatible polymer. Such groups may be represented by the general formula VII

15



20

in which A^5 is a valence bond, $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$, preferably $-\text{O}-$, R^{16} is a valence bond (optionally together with A^5) or alkanediyl, $-\text{C}(\text{O})\text{alkylene-}$ or $-\text{C}(\text{O})\text{NHalkylene}$, preferably alkanediyl and preferably containing from 1 to 6 carbon atoms; and

25

the groups R^{17} are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or two or three of the groups R^{17} , together with the nitrogen to which they are attached, form a heterocyclic ring of from 5 to 7 atoms, or the three group R^{17} together with the nitrogen atom to which they are attached form a fused ring heterocyclic structure containing from 5 to 7 atoms in each ring.

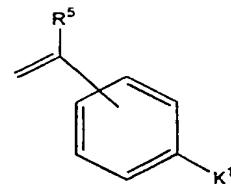
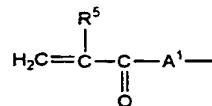
Preferably the monomers used to form the polymer include a surface binding monomer having the general formula II



II

wherein Y^1 is selected from

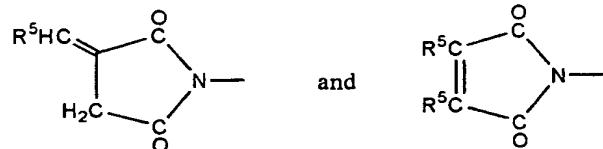
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10 $\text{CH}_2=\text{C}(\text{R}^5)-\text{CH}_2-\text{O}-$, $\text{CH}_2=\text{C}(\text{R}^5)-\text{CH}_2-\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R}^5)\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R}^5)-$

$\text{O}-$, $\text{CH}_2=\text{C}(\text{R}^5)\text{CH}_2\text{OC}(\text{O})\text{N}(\text{R}^6)-$, $\text{R}^7\text{OOC}\text{R}^5=\text{CR}^5\text{C}(\text{O})-\text{O}-$,

15 $\text{R}^5\text{CH}=\text{CHC}(\text{O})\text{O}-$, $\text{R}^5\text{CH}=\text{C}(\text{COOR}^7)\text{CH}_2-\text{C}(\text{O})-\text{O}-$,



15 wherein:

R^5 is hydrogen or a $\text{C}_{1\text{-}}\text{C}_4$ alkyl group;

R^6 is hydrogen or a $\text{C}_{1\text{-}}\text{C}_4$ alkyl group or R^6 is R^4 ;

R^7 is hydrogen or a $\text{C}_{1\text{-}}\text{C}_4$ alkyl group;

A^1 is $-\text{O}-$ or $-\text{NR}^6-$; and

20 K^1 is a group $-(\text{CH}_2)_q\text{OC}(\text{O})-$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{O}-$,

$-(\text{CH}_2)_q\text{OC}(\text{O})\text{O}-$, $-(\text{CH}_2)_q\text{NR}^8-$, $-(\text{CH}_2)_q\text{NR}^8\text{C}(\text{O})-$,

$-(\text{CH}_2)_q\text{C}(\text{O})\text{NR}^8-$, $-(\text{CH}_2)_q\text{NR}^8\text{C}(\text{O})\text{O}-$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{NR}^8-$,

$-(\text{CH}_2)_q\text{NR}^8\text{C}(\text{O})\text{NR}^8-$ (in which the groups R^8 are the same or different),

$-(\text{CH}_2)_q\text{O}-$, $-(\text{CH}_2)_q\text{SO}_3-$, or a valence bond

25 q is from 1 to 12;

and R^8 is hydrogen or a $\text{C}_{1\text{-}}\text{C}_4$ alkyl group;

and R^4 is a surface binding group, selected from hydrophobic groups, ionic groups, reactive groups capable of forming covalent bonds with surface functional groups on the surface of the tube and crosslinkable groups

30 capable of forming intermolecular crosslinks, optionally in conjunction with curing agents.

In the binding monomer of the general formula II, the group R⁴ is preferably

a) a straight or branched alkyl, alkoxyalkyl or oligoalkoxyalkyl chain containing 6 or more, preferably 6 to 24 carbon atoms, unsubstituted or substituted by one or more fluorine atoms optionally containing one or more carbon carbon double or triple bonds; or

5 b) a siloxane group -(CR^{18a}₂)_{qq}(SiR¹⁹₂)(OSiR¹⁹₂)_{pp}R¹⁹ in which each group R¹⁸ is the same or different and is hydrogen or alkyl of 1 to 4 carbon atoms, or aralkyl, for example benzyl or phenethyl, each group R¹⁹ is alkyl of 10 1 to 4 carbon atoms, qq is from 1 to 6 and pp is from 0 to 49; or

c) a crosslinkable group, capable of reacting with the groups of the same definition, or with groups of a different definition provided by a mixture of monomers of the general formula II, having different groups R⁴.

Preferred crosslinkable groups have the formula -R²⁰Q, where

15 R²⁰ is a valence bond or, more preferably, a straight or branched alkanediyl, alkylenoxyalkylene or alkylene(oligooxyalkylene) group and

Q is a reactive group selected from cinnamyl, epoxy, -CHOHCH₂Hal (in which Hal is a halogen atom), methylol, silyl and siloxyl groups containing one or more reactive substituents such as halogen, for example chlorine, or 20 alkoxy, generally containing from 1 to 4 carbon atoms, for example methoxy or ethoxy, hydroxyl, amino, carboxyl, ethylenically acetylenically unsaturated crosslinkable groups, acetoacetoxy, chloroalkylsulphone, succinimido, tosylate, triflate, imidazolecarbonylamo or optionally substituted triazine groups.

25 Most preferred definitions of R⁴ are C₈₋₁₈-alkyl, -alkenyl or -alkynyl, optionally including fluorine substituents, and mixtures of different groups - R²⁰-Q, in which the groups R²⁰ are the same or different and each represent C₂₋₆-alkanediyl, and one of the groups Q is hydroxyl and the other is a reactive silyl group, preferably having the formula Si(OR²²)₃, where each 30 group R²² is C₁₋₄-alkyl, preferably methyl or ethyl and n is 0 or 1. A suitable mixture of two comonomers of the formula II is of hydroxyalkylmethacrylate and trimethoxysilylalkyl methacrylate, preferably in which both alkanediyl

groups R^{20} are the same and are, most preferably, propyl. Preferably the monomers include hydrophobic surface binding group containing monomers and cross-linkable group containing monomers.

In monomers of the formula I and II, Y and Y^1 are preferably 5 $H_2C=C(R)C(O)A^-$ and $H_2C=C(R^5)C(O)A^1-$, respectively. R and R^5 are preferably hydrogen or, more preferably, methyl. A and A^1 are preferably the same and are most preferably $-O-$.

B is preferably C_{2-18} , more preferably C_{2-6} -alkanediyl, branched, or, preferably, straight chain, that is $(CH_2)_r$, where r is 2 to 18, preferably 2 to 6.

10 The ethylenically unsaturated monomers may include diluent monomers, for instance which may be added to adjust the solubility of the polymer in the coating composition from which it is coated, to adjust the hydrophilicity/phobicity, to control the flexibility of the coating, or for other reasons. Such monomers are generally non-ionic. Suitable diluent 15 monomers are alkyl(alk)acrylates, for instance having 1 to 4 carbon atoms in the alkyl group, N-alkyl- or N,N-dialkyl(alk)acrylamides, for instance having 1 to 4 carbon atoms in the or each alkyl group, (alk)acrylamide, hydroxylalkyl(alk)acrylates, for instance having 1 to 6 carbon atoms in the alkyl group, vinyl lactams, such as vinylpyrrolidone, and styrene. Mixtures 20 may be used.

25 The ethylenically unsaturated monomers from which the polymer having zwitterionic moieties is formed may include other functional monomers. For instance monomers having functional groups may provide attachment points for ligands such as pharmaceutically active agents, specific binding moieties, or antithrombogenic agents. Comonomers may alternatively include ionic groups, for instance for providing electrostatic attraction with counterionically charged moieties desired to be bonded to the coating. For instance cationic or cationisable monomers may allow loading 30 of the zwitterionic polymer coating of the graft by anionically charged mucopolysaccharides such as heparin, which may reduce thrombogenicity of the graft still further.

Preferably the zwitterionic monomer is used in the monomer mixture in a molar proportion of at least 1%, preferably less than 75%, more preferably in the range 5 to 50%, most preferably 10-33%. The surface binding monomer is generally used in molar proportion of at least 2%, 5 preferably at least 5% or at least 10%, more preferably in the range 15 to 99%. Where the surface binding monomers provide cross-linkability, the level of reactive cross-linkable groups is preferably in the range 5 to 33%. Where the surface binding monomer comprises hydrophobic physisorbable groups, it is preferably present in a molar amount in the range 50 to 99%, 10 more preferably 60-95%.

In a particularly preferred embodiment of the invention the polymer used is as described in our co-pending application publication number WO-A-98/30615.

Where the polymer is formed from monomer including reactive groups 15 Q, in the kit of the invention, such groups have been reacted to provide covalent bonds to the underlying surface functional groups, and/or intermolecular and intramolecular crosslinking. It is particularly preferred in the invention that the monomers include crosslinkable groups Q and the in the novel kit, the polymer has been subjected to conditions whereby 20 crosslinking has taken place. Crosslinking improves the coherent strength of the coating and hence the retention of the stent on the balloon.

The kit of the invention should be sterile or sterilizable. The kit may be provided in a closed package, and is preferably sterile within the package. Whilst sterilization maybe achievable by sterilizing the individual 25 components, or by sterilizing the partially assembled device, for instance the balloon catheter/stent combination and, separately, the coating composition, preferably the coated kit is subjected to sterilization.

Sterilization maybe by subjecting the device to high temperature and pressures, for instance in an autoclave, by exposure to irradiation, or 30 preferably, by treatment with ethylene oxide gas.

The present inventors have found that exposure of certain useful polymers to ethylene oxide gas may result in improvement in the function of

the polymer to retain the stent on the balloon. Thus when the polymer having the preferred groups Q comprising reactive silyl groups of the formula $\text{Si}(\text{OR}^{22})_3$, contacting the polymer with ethylene oxide, before, during, after or instead of subjecting the polymer to any other crosslinking conditions, result 5 in improved stent retention.

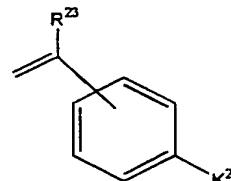
It is believed that polymers having pendent reactive silyl groups of the formula $\text{Si}(\text{OR}^{22})_3$ have not previously been contacted with gaseous ethylene oxide to provide curing of the polymer. According to a second aspect of the invention therefore there is provided a curing process in which a polymer 10 having pendent groups of the formulae $\text{Si}(\text{OR}^{26})_3$, in which each group R^{26} is independently selected from $\text{C}_{1,4}$ -alkyl, is contacted with gaseous ethylene oxide to provide a cured polymer.

In this aspect of the invention, the silyl group is generally introduced by forming the polymer from ethylenically unsaturated monomers including a 15 monomer of the formula VIII

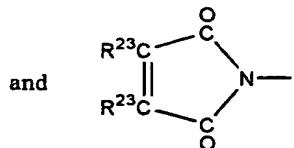
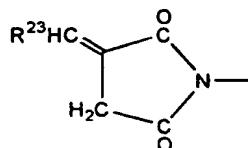


wherein

Y^2 is selected from



20 $\text{CH}_2=\text{C}(\text{R}^{23})-\text{CH}_2-\text{O}-$, $\text{CH}_2=\text{C}(\text{R}^{23})-\text{CH}_2\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R}^{23})\text{OC}(\text{O})-$,
 25 $\text{CH}_2=\text{C}(\text{R}^{23})-\text{O}-$, $\text{CH}_2=\text{C}(\text{R}^{23})\text{CH}_2\text{OC}(\text{O})\text{N}(\text{R}^{24})-$, $\text{R}^{25}\text{OOC}\text{R}^{23}=\text{CR}^{23}\text{C}(\text{O})-\text{O}-$,
 $\text{R}^{23}\text{CH}=\text{CHC}(\text{O})\text{O}-$, $\text{R}^{23}\text{CH}=\text{C}(\text{COOR}^{25})\text{CH}_2\text{C}(\text{O})-\text{O}-$,



30

wherein:

R^{23} is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group;

R²⁴ is hydrogen or a C₁-C₄ alkyl group or R²⁴ is R³⁰Q¹;

R²⁵ is hydrogen or a C₁₋₄ alkyl group;

A⁷ is -O- or -NR²⁴-; and

K² is a group -(CH₂)_tOC(O)-, -(CH₂)_tC(O)O-,

5 - (CH₂)_tOC(O)O-, -(CH₂)_tNR²⁸-, -(CH₂)_tNR²⁸C(O)-, -(CH₂)_tC(O)NR²⁸-, -(CH₂)_tNR²⁸C(O)O-, -(CH₂)_tOC(O)NR²⁸-, -(CH₂)_tNR²⁸C(O)NR²⁸- (in which the groups R²⁸ are the same or different), -(CH₂)_tO-, -(CH₂)_tSO₃ -, or a valence bond

t is from 1 to 12;

10 and R²⁸ is hydrogen or a C₁-C₄ alkyl group;

R³⁰ is a straight or branched C₂₋₂₄ alkanediyl group, or a alkyleneoxaalkylene or alkylene(oligo-oxaalkylene) group in which each alkylene has 2 to 12 carbon atoms, and

15 Q¹ is a group Si(OR²⁶)₃

the groups R²⁶ are independently selected from C₁₋₄ alkyl groups.

Preferably each of the groups R²⁶ are C₁ or 2-alkyl, most preferably methyl.

In groups R³⁰, an alkyleneoxealkylene or alkylene(oligo-oxaalkylene) group, has alkylene groups of 2 to 3 carbon atoms, most preferably 2 carbon atoms. Most preferably R³⁰ is an alkanediyl group, most preferably having 2 to 6 carbon atoms, most preferably 3 or 4 carbon atoms. Most preferably it is a group (CH₂)_{2 to 4}-alkyl group.

25 Preferably the polymer is formed from ethylenically unsaturated monomers also including monomer of the formula I described above. The monomers preferably also include a monomer of the formula II above in which the group Q is a crosslinkable group of the formulae R²⁰ Q in which Q is a hydroxyl group. R²⁰ maybe any of the groups defined above for R³⁰.

30 Ethylene oxide contact is generally conducted under conditions used for sterilization procedures. For instance gas is contacted with the polymer for a period of at least an hour, more preferably at least 2 hours for instance up to 12 hours or even more, at a temperature of at least 40C, more

preferably at least 45C up to 70C, most preferably 45-55C, optionally in the presence of steam and usually with a diluent, carrier gas of nitrogen or another inert gas. The proportion in the total gas of ethylene oxide is preferably at least 50%, more preferably at least about 80%. Treatment 5 may conveniently be carried out under reduced pressure. After treatment the residual ethylene oxide is removed and then the polymer is usually blanketed by nitrogen and washed with air, for instance in several steps.

The invention provides also a method of producing the novel kit by coating an assembly consisting of a balloon catheter having a stent mounted 10 on the balloon with a liquid coating composition containing a film forming polymer, and then curing the coating composition.

The process is generally carried out by dipping the assembly into a volume of the liquid composition, preferably so that the entire stent is immersed within the volume of liquid. Where only partial coating is required, 15 the assembly may be dipped to a depth whereby the portion to be desired is immersed in the liquid. Where it is desired to coat discrete areas of the surface, for instance discrete axially separated rings on the surface, it is convenient for the composition to be applied by spraying.

The liquid coating composition preferably comprises a film forming 20 polymer and a solvent in which the polymer is dissolved or dispersed. Curing generally comprises removal of the solvent, for instance by evaporation under raised temperature and/or reduced pressure.

Curing preferably also comprises crosslinking of a crosslinkable polymer in the coating composition. Crosslinking may be carried out before, 25 during and/or after solvent removal. Crosslinking of a polymer which includes crosslinkable groups (as described above) involves subjecting the polymer to conditions under which the crosslinkable groups react to form inter-and intra molecular bonds. Such conditions generally involve heating the polymer, exposing it to incident actinic radiation and/or to moisture or gaseous crosslinking agents. Such agents may include ethylene oxide.

Preferably the method includes the step of sterilizing the coated assembly. Sterilization may be carried out simultaneously with curing and/or

crosslinking steps. Sterilization may involve subjecting the coated assembly to raised temperature and/or pressure, irradiating the assembly and/or contacting the coated assembly with ethylene oxide. Preferably sterilization is carried out by contacting the coated assembly with ethylene oxide under 5 the conditions described above in connection with the second aspect of the invention.

Most balloon catheters comprise a guidewire lumen so that the catheter can be run on a pre-positioned guidewire for navigation through the desired body lumens. In the present invention it may be desirable to coat 10 the inside of the body lumen with the same type of coating as the exterior surface of the stent and balloon. The method therefore it maybe desirable to allow the coating composition to coat the guide wire lumen, for instance by leaving the lumen open during a dipping step and/or by directing liquid compositions through the lumen during a dipping or spraying process. 15 Alternatively it maybe desired to avoid coating the guidewire lumen, for instance to avoid reducing the internal diameter of the lumen. In this case, the lumen may be blocked during the coating process using a suitable bung.

In the kit of the invention the coherent coating should have a thickness which avoids increasing the external diameter of the kit by an 20 unacceptable amount, but which has adequate thickness to provide mechanical strength to improve retention of the stent by the desired amount. The thickness should not be so high as increase the pressure at which the balloon deploys the stent. The coating thickness, on the stent external surface, is preferably in the range 5 to 500nm, most preferably in the range 25 10 to 200nm, for instance in the range 20 to 100nm. The coating may have the same thickness on the balloon and on the stent or may be thicker on the surface of the balloon.

The coating thickness maybe adjusted as desired by controlling the rheology of the liquid coating composition, for instance by controlling the 30 concentration, by selecting suitable coating conditions, for instance in terms of temperature, number of coatings of liquid composition applied, or by selecting suitable drying conditions, for instance in terms of the conditions

under which excess liquid coating composition is allowed to drain from the stent, as well as conditions of temperature and/or reduced pressure.

In the method, the coating composition preferably has a polymer concentration in the range 2 to 50 g/l, most preferably in the range 5 to 25 g/l, for instance in the range 10 to 20 g/l.

The solvent in the coating composition is, for instance, an alcohol (including glycol), ether, water, alkane or mixtures. Preferably the solvent consists of ethanol, optionally with glycol, mixed with water or with alkane.

The stent is generally formed from a metallic tube provided with 10 openings to confer balloon expandability. Alternatively the stent may be formed from bent or braided wires. Preferred stents have a wall thickness in the range 0.5 to 2.5 mm, most preferably being at least 1000 times the thickness of the coating (average). Preferably the stent is formed from stainless steel. It will often already be provided with an overall coating of 15 biocompatible material. The overall coating may be formed of the same or different polymer as the polymer in the coating. It suitable has a thickness such that the total polymer coating thickness including the coherent film is less than 500nm thick, for instance less than 250nm thick.

We have found that the provision of a polymer coating on the outside 20 of the stent/balloon catheter assembly provides improved retention of the stent on the catheter when subjected to axially directed forces, without any deterioration in the ability of the stent to be deployed effectively. The coating does not adversely effect the burst pressures of the balloons, nor the pressures to which the balloons needed to be inflated to achieve stent 25 deployment. Since the coatings are biocompatible, and indeed have already been approved for use for coating stents for long term implantation, the biocompatibility will not be compromised.

The invention is illustrated further in the following examples.

30 **Example 1**

The polymer used for this example was simplified as described in WO-A-98/30615, polymer 05. The polymer was formed from 2-

(methacryloyloxyethyl)-2'-(trimethylammoniumethyl) phosphate inner salt: dodecyl methacrylate: 3-hydroxypropyl methacrylate: 3-trimethoxysilylpropyl methacrylate in molar ratios of 23:47:25:5. Solutions of the polymer were made up in ethanol at different polymer concentrations. The test assemblies 5 comprised Divsio stents, with (unexpanded outer) diameter 1.6mm, length 28mm and wall thickness 0.914mm, formed of stainless steel and provided with a biocompatible coating comprised of the same polymer as used in this example on all surfaces at a coating thickness of about 20-100um, mounted on a Nycomed Copan balloon catheter having a 30mm balloon having an 10 expanded diameter (at 6 atm (6×10^5 Pa)) of 3.5mm. The stents were crimped onto the balloons of the balloon catheters using a standard crimping device with jaws of 0.036 in (0.91 mm) at a pressure of 80psi (5.5×10^5 Pa), all stents being mounted under the same conditions. The guidewire lumen of the balloon catheter was blocked using a suitably sized stylet.

15 The assembly of stent and balloon catheter was coated by dipping to a depth such that the stent was completely immersed in a volume of coating composition and then withdrawn vertically upwardly at a rate of 1.75-1.85mm s⁻¹. The coated assemblies were dried and cured by heating to 70°C for 4 hours.

20 The coated assemblies were then subjected to tests to determine the retention of the stent on the balloon and stent deployment. Different samples were used for the different tests.

25 The retention of the stent onto the balloon was measured by gripping the distal end of the catheter and drawing it through a 1.0mm orifice, which is too small for the stent to pass through. The force is thus exerted in a direction to shift the stent proximally. The retention values are set out in table 1 below, which shows the mean retention for 4 samples coated from different concentrations of polymer as specified, as well as the percentage increase in retention.

Table 1

Polymer Concentration (g/l)	Mean Retention (N)	% increase in retention compared to control
Control	2.93	
2.0	2.75	-6.0
6.0	3.78	25.1
8.0	4.53	55.5
10.0	4.71	61.5

10

Example 2

Assemblies coated as in example 1 with 10 g/l of the same polymer were subjected to tests of their deployment characteristics. The balloon catheter was inflated in 0.5 atmosphere (50 kPa) increments using a 15 Bundenberg pressure gauge. The results of the individual tests are reported in table 2.

For each of the stents, there was gradual, immediate and even detachment of the stent from the balloon at full deployment. Following deployment there was free movement of the balloon from the stent for each 20 of the samples. In no instances does the balloon burst during deployment.

25

30

Table 2

Stent ID	Deployment Pressure (Atm)	Deployment Extent
1	1.0	a
	1.5	c
	2.0	e
2	1.0	b
	1.5	c
	2.0	e
3	1.0	b
	1.5	c
	2.0	d
	2.5	e
4	1.0	b
	1.5	c
	2.0	d
	2.5	e
5	1.0	a
	1.5	c
	2.0	d
	2.5	e
6	1.0	a
	1.5	c
	2.0	d
	2.5	e

10

Key

- a: no change
- b: slight inflation of the balloon
- c: stent flared, balloon slightly inflated at end
- d: partial inflation of the balloon, and flaring of stent end
- e: immediate (within about 5s) full deployment

15

The coated stents were also characterised for their total coating thickness using atomic force microscopy. This indicated the mean coating thickness for the stent of the kit of the invention is about 80 nm, whilst that of the starting stents is about 50 nm. The extra thickness from the coherent 5 coating used in the invention over the mounted stent is thus believed to be about 30 nm.

The specification for the balloon catheter requires that the stent should fully deploy at 8 atmospheres or less. The results taken as a whole indicate that each sample deploys satisfactorily. In combination with the 10 results of example 1, this shows that the overcoating increases retention of the stent without adversely effecting the deployment characteristics.

Example 3

Further assemblies of stents mounted on balloon catheters were 15 coated using the 10 g/l polymer composition in ethanol, dried and cured using the same conditions as in example 1. In the example the coated assemblies were sterilized using a ethylene oxide sterilization cycle in which a small amount of steam is introduced into the chamber of the sterilizing device followed by a higher amount of ethyleneoxide. The assemblies are 20 maintained in contact with the gas for a period of 5 hours at a pressure of about 350Pa and a temperature of 50C. Following exposure to the gas the gas is removed by evacuating the chamber then the chamber is filled sequentially with nitrogen and then clean volumes of air in several steps.

The retention values were measured using a technique similar to that 25 used in example 1, but in which the stent was subjected to a force to move is distally rather than proximally. The coated assemblies were compared with control, uncoated assemblies.

The results are shown in table 3 below.

Table 3

Sample	Retention		
	Mean (n=4)(N)	St.Dev(N)	% increase
Control	1.55	0.19	
Invention	3.68	0.40	137

The results indicate that ethylene oxide treatment following curing leads to a greater increase in stent retention than coating and crosslinking by heating alone.

Example 4

Further samples of the coated assemblies produced in example 3 were subjected to the deployment test described in example 1. Subsequent to the deployment tests, the balloons were and inflated up to failure. The balloons from the tests of example 3 were also subsequently inflated to failure.

The deployment tests indicate satisfactory deployment very similar to stents 3 to 6 in Example 1. Thus all tested samples were fully deployed at 2.5 atmosphere, within 5 seconds of the imposition of the pressure.

The results of the burst tests are shown in table 4. Samples 4.1 to 4.4 had been subjected to retention tests whilst samples 4.5 and 4.6 had been subjected to deployment tests.

Table 4

Sample	Burst Pressure (atm/10⁵Pa)	Failure Mode
4.1	18.0	Pinhole
4.2	20.0	Axial split
4.3	20.0	Axial split
4.4	18.0	Pinhole
4.5	19.7	Axial split
4.6	20.4	Axial split

The "pinhole" failures observed were caused by the piercing of the balloon during measurement of the retention values. It is considered unlikely that the pinholes in the balloons were caused by the overcoating. Since it is unlikely that the stent will be subjected to forces as high as those required to dislodge the stent from the balloon during normal use, it is believed that the pinholes in the balloons were caused by the overcoating. The average burst pressure of balloons having been used to deploy stents is about $20-22 \times 10^5$ Pa. The coating appears not to reduce this. In any event all pressures recorded at failure were higher than the minimum pressure required in a product specification which is 16 atm (10^5 Pa).

Example 5

Further sampling of the stent/catheter assembly used in the previous examples were coated with a copolymer of 2-methacryloyloxyethyl-2'-trimethyl ammoniumethyl phosphate inner salt: dodecyl-methacrylate 1:2 (molar) synthesised substantially as in example 1 of WO-A-9301221) from a 10 g/l solution in ethanol. The coated assemblies (without prior sterilisation) were subjected to the retention test. The retention rates were about 60% higher than those of the control.

20

Example 6

Overcoating with alternative polymers

Alternative polymer overcoating systems were evaluated using 15mm DivYsio stents that had been crimped onto nylon 6,6 filament (1mm diameter, Goodfellow) as a model for the nylon balloon catheter. This model is formed of the same polyamide as the balloon and has approximately the same diameter. The stent/filament combination was dip-coated at 3mm/sec into a solution of the polymer under study dissolved in an appropriate solvent and left to air dry for 30 minutes. The sample was then oven dried at 70C overnight prior to determining the extent of retention. The

retention values were determined using a technique similar to that used in example 1.

Table 5

Polymer/Sample	Solvent Concentration	Mean (n=6) (N)	St. Dev (N)	% Increase
Non Overcoated Control	-	0.0725	0.023	-
PC Coated (Example 1)	10g/L Ethanol	2.967	0.557	3992
PEG 10,000 (Aldrich)	10g/L (90:10) Ethanol:water	0.665	0.158	817
TECOFLEX (Thermedics)	10g/L THF	0.158	0.066	118
Hydroxyethylcellulose (Cellusize, Union Carbide)	1g/L water	0.102	0.034	40

15

The results show that similar increases in retention can be obtained using a variety of polymer samples, including water-soluble systems, biological macromolecules and synthetic polymers.

Claims

1. A kit comprising a balloon catheter comprising a balloon at or near its distal end, and a stent mounted on the balloon, characterized in that in that the exterior surface of the balloon and stent are provided with a coherent coating comprising a film-forming polymer.
- 5 2. A kit according to claim 1 in which the coating is continuous around the circumference of the exterior surface of the balloon and stent over at least a portion of the axial extent of that section.
3. A kit according to claim 1 or claim 2 in which the coating extends 10 along the entire axial length of the stent, preferably beyond both ends thereof.
4. A kit according to any preceding claim in which the polymer of the coating is cross-linked.
5. A kit according to any preceding claim in which the polymer has 15 pendent zwitterionic groups.
6. A kit according to claim 5 in which the polymer is formed from ethylenically unsaturated monomers including a zwitterionic monomer of the general formula I:



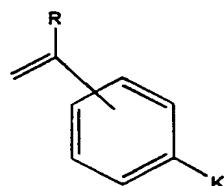
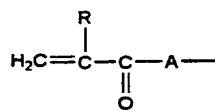
20 wherein

B is a straight or branched alkylene (alkanediyl), alkyleneoxaalkylene or alkylene oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X or Y contains a terminal carbon atom bonded to B, a valence bond;

25 X is a zwitterionic group; and

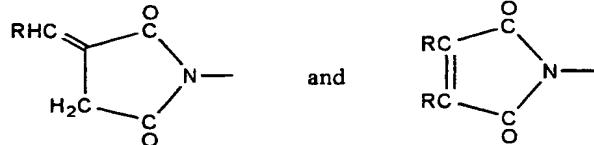
Y is an ethylenically unsaturated polymerisable group selected from

30



$\text{CH}_2=\text{C}(\text{R})-\text{CH}_2-\text{O}-$, $\text{CH}_2=\text{C}(\text{R})-\text{CH}_2\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R})\text{OC}(\text{O})-$, $\text{CH}_2=\text{C}(\text{R})-\text{O}-$,
 $\text{CH}_2=\text{C}(\text{R})\text{CH}_2\text{OC}(\text{O})\text{N}(\text{R}^1)-$, $\text{R}^2\text{OOC}\text{R}=\text{CRC}(\text{O})-\text{O}-$, $\text{RCH}=\text{CHC}(\text{O})\text{O}-$,
 $\text{RCH}=\text{C}(\text{COOR}^2)\text{CH}_2-\text{C}(\text{O})-\text{O}-$,

5



and

wherein:

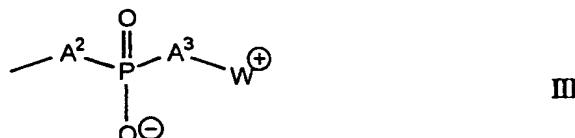
10 R is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group;
 R^1 is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group or R^1 is $-\text{B-X}$ where B and X are as defined above; and

15 R^2 is hydrogen or a C_{1-4} alkyl group;
 A is $-\text{O-}$ or $-\text{NR}^1-$;
 K is a group $-(\text{CH}_2)_p\text{OC}(\text{O})-$, $-(\text{CH}_2)_p\text{C}(\text{O})\text{O}-$,
 $-(\text{CH}_2)_p\text{OC}(\text{O})\text{O}-$, $-(\text{CH}_2)_p\text{NR}^3-$, $-(\text{CH}_2)_p\text{NR}^3\text{C}(\text{O})-$,
 $-(\text{CH}_2)_p\text{C}(\text{O})\text{NR}^3-$, $-(\text{CH}_2)_p\text{NR}^3\text{C}(\text{O})\text{O}-$, $-(\text{CH}_2)_p\text{OC}(\text{O})\text{NR}^3-$,
 $-(\text{CH}_2)_p\text{NR}^3\text{C}(\text{O})\text{NR}^3-$ (in which the groups R^3 are the same or different),
 $-(\text{CH}_2)_p\text{O-}$, $-(\text{CH}_2)_p\text{SO}_3-$, or, optionally in combination with B , a valence bond
 p is from 1 to 12; and

20 R^3 is hydrogen or a $\text{C}_1\text{-C}_4$ alkyl group.

7. A kit according to claim 6 in which X is a group having the general formula III

25



in which the moieties A^2 and A^3 , which are the same or different, are $-\text{O-}$, $-\text{S-}$, $-\text{NH-}$ or a valence bond, preferably $-\text{O-}$, and W^+ is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is preferably a C_{1-12} -alkanediyil group,

preferably in which W^+ is a group of formula

-W¹-N⁺R⁹₃, -W¹-P⁺R¹⁰₃, -W¹-S⁺R¹⁰₂ or -W¹-Het⁺ in which:

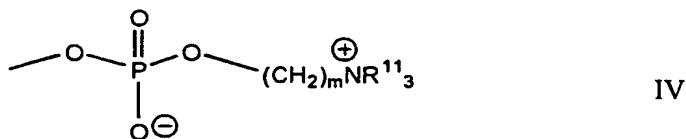
W¹ is alkanediyl of 1 or more, preferably 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, or alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene or alkylene cycloalkyl alkylene, which group W¹ optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups R⁹ are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, preferably methyl, or aryl, such as phenyl, or two of the groups R⁹ together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups R⁹ together with the nitrogen atom to which they are attached form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups R⁹ is substituted by a hydrophilic functional group, and

the groups R¹⁰ are the same or different and each is R⁹ or a group OR⁹, where R⁹ is as defined above; or

Het is an aromatic nitrogen-, phosphorus- or sulphur-, preferably nitrogen-, containing ring, for example pyridine.

8. A kit according to claims 7 in which X is a group having the general formula IV:



where the groups R¹¹ are the same or different and each is hydrogen or C₁₋₄ alkyl, and m is from 1 to 4, in which preferably the groups R¹¹ are the same preferably methyl.

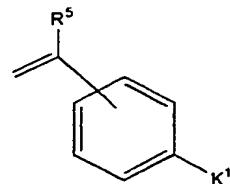
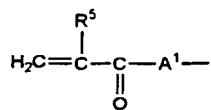
9. A kit according to any of claims 4 to 9 in which the monomers used to form the polymer include a surface binding monomer having the general formula II

Y^1R^4

II

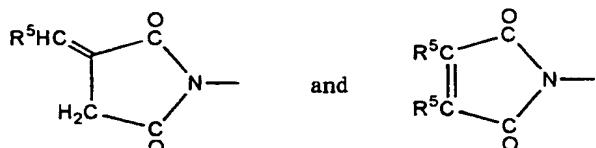
wherein Y^1 is selected from

5



10 $CH_2=C(R^5)-CH_2-O-$, $CH_2=C(R^5)-CH_2 OC(O)-$, $CH_2=C(R^5)OC(O)-$, $CH_2=C(R^5)-O-$,
 $CH_2=C(R^5)CH_2OC(O)N(R^6)-$, $R^7OOCR^5=CR^5C(O)-O-$,
 $R^5CH=CHC(O)O-$, $R^5CH=C(COOR^7)CH_2-C(O)-O-$,

15



wherein:

R^5 is hydrogen or a C_1-C_4 alkyl group;
 R^6 is hydrogen or a C_1-C_4 alkyl group or R^6 is R^4 ;
 R^7 is hydrogen or a C_{1-4} alkyl group;
20 A^1 is $-O-$ or $-NR^6-$; and
 K^1 is a group $-(CH_2)_qOC(O)-$, $-(CH_2)_qC(O)O-$,
 $-(CH_2)_qOC(O)O-$, $-(CH_2)_qNR^8-$, $-(CH_2)_qNR^8C(O)-$,
 $-(CH_2)_qC(O)NR^8-$, $-(CH_2)_qNR^8C(O)O-$, $-(CH_2)_qOC(O)NR^8-$,
 $-(CH_2)_qNR^8C(O)NR^8-$ (in which the groups R^8 are the same or different),
25 $-(CH_2)_qO-$, $-(CH_2)_qSO_3-$, or a valence bond
 q is from 1 to 12;
and R^8 is hydrogen or a C_1-C_4 alkyl group;
and R^4 is a surface binding group, selected from hydrophobic groups, ionic groups, reactive groups capable of forming covalent bonds with surface 30 functional groups on the surface of the tube and crosslinkable groups capable of forming intermolecular crosslinks, optionally in conjunction with curing agents.

10. A kit according to any of claims 4 to 9 in which the polymer is formed from ethylenically unsaturated monomers including a monomer of formula VIII



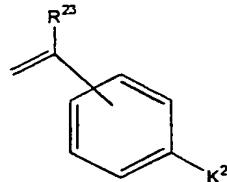
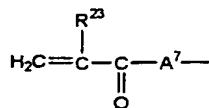
VIII

5

wherein

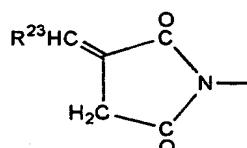
 Y^2 is selected from

10

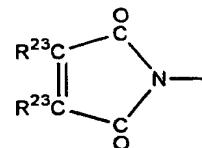


$CH_2=C(R^{23})-CH_2-O-$, $CH_2=C(R^{23})-CH_2 OC(O)-$, $CH_2=C(R^{23})OC(O)-$,
 $CH_2=C(R^{23})-O-$, $CH_2=C(R^{23})CH_2OC(O)N(R^{24})-$, $R^{25}OOC R^{23}=CR^{23}C(O)-O-$,
 $R^{23}CH=CHC(O)O-$, $R^{23}CH=C(COOR^{25})CH_2-C(O)-O-$,

15



and



wherein:

20

 R^{23} is hydrogen or a C_1-C_4 alkyl group; R^{24} is hydrogen or a C_1-C_4 alkyl group or R^{24} is $R^{30} Q^1$; R^{25} is hydrogen or a C_{1-4} alkyl group; A^7 is $-O-$ or $-NR^{24}-$; and K^2 is a group $-(CH_2)_tOC(O)-$, $-(CH_2)_tC(O)O-$,

25

 $-(CH_2)_tOC(O)O-$, $-(CH_2)_tNR^{28}-$, $-(CH_2)_tNR^{28}C(O)-$, $-(CH_2)_tC(O)NR^{28}$, $-(CH_2)_tNR^{28}C(O)O-$, $-(CH_2)_tOC(O)NR^{28}-$, $-(CH_2)_tNR^{28}C(O)NR^{28}-$ (in which the groups R^{28} are the same or different), $-(CH_2)_tO-$, $-(CH_2)_tSO_3-$, or a valence bond t is from 1 to 12;

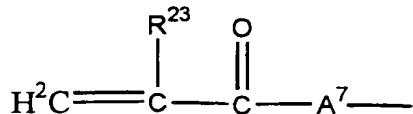
30

and R^{28} is hydrogen or a C_1-C_4 alkyl group;

R^{30} is a straight or branched C_{2-24} alkanediyl group, or a alkyleneoxaalkylene or alkylene(oligo-oxaalkylene) group in which each alkylene has 2 to 12 carbon atoms, and

5 Q^1 is a group $Si(OR^{26})_3$ in which the groups R^{26} are independently selected from C_{1-4} alkyl groups.

11. A kit according to claim 10 in which Y^2 is



10 in which R^{23} is preferably methyl, and A^7 is preferably -O-, and in which R^{30} is C_{2-6} alkanediyl and each R^{26} is C_{1-2} -alkyl, preferably methyl.

12. A kit according to any preceding claim which is sterile, preferably sterilised by ethylene oxide treatment.

13. A kit according to any preceding claim in which the luminal surface of the guidewire lumen has not been provided with the said coherent coating.

14. A kit according to any preceding claim in which the stent is formed from a metal tube, preferably of stainless steel.

15. A method in which an assembly comprising a balloon catheter and, mounted on the balloon of the balloon catheter, a stent is coated with a 20 liquid coating composition containing a film-forming polymer, and the coating composition is then cured to leave a coherent film of polymer on the exterior surface of the stent and balloon.

16. A method according to claim 15 in which in the coating step the balloon and stent assembly is dipped into the liquid composition.

25 17. A method according to claim 16 in which the catheter has a guidewire lumen passing through the balloon and the lumen is blocked during the dipping step.

18. A method according to any of claims 15 to 17 in which curing involves removal of solvent from the coating composition, preferably by evaporation.

19. A method according to claim 18 in which the solvent in the coating composition comprises water, alcohol, ether, or alkane or mixtures, preferably ethanol in admixture with water or alkane.
20. A method according to any of claims 15 to 19 in which the film-forming polymer is cross-linkable and the curing step includes a step of cross-linking the polymer.
5
21. A method according to claim 20 in which the polymer is as defined in claim 10 or claim 11.
22. A method according to any of claims 15 to 21 in which the coated assembly is sterilised by contact with ethylene oxide.
10

INTERNATIONAL SEARCH REPORT

Inte... Application No
PCT/GB 00/02485

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 920 843 A (BOSTON SCIENT CORP) 9 June 1999 (1999-06-09) cited in the application column 2, line 30 - line 44 column 11, line 27 - line 41 claims; figures —	1-22
Y	WO 93 01221 A (BIOCOMPATIBLES LTD) 21 January 1993 (1993-01-21) cited in the application page 65, line 23 - line 27 claims; examples —	1-22
X	WO 98 30615 A (BIOCOMPATIBLES LTD) 16 July 1998 (1998-07-16) cited in the application page 14, line 35 -page 15, line 8 claims; examples —	1-22 —/—

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Patent family members are listed in annex.

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Date of the actual completion of the international search

7 September 2000

Date of mailing of the international search report

18/09/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kuehne, H-C

INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/GB 00/02485

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 344 426 A (LAU LILIP ET AL) 6 September 1994 (1994-09-06) claims; figures _____	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No.

PCT/GB 00/02485

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